Role of Angiogenic and Inflammatory Signal Pathways in Psoriasis

Xiao-Yong Man[1] and Min Zheng[1]

The Journal of Investigative Dermatology Symposium (2015) **17,** 43–45; doi:10.1038/jidsymp.2015.22

Dysregulation of any of the factors involved in the inflammatory response is important in the development of disease, and failure to resolve this response leads to chronic inflammation. Psoriasis is a common immune-mediated chronic inflammatory skin disease characterized by epidermal hyperplasia, parakeratosis, dermal inflammatory cell infiltration, and angiogenesis (Nestle *et al.*, 2009). There is increased growth and altered differentiation of keratinocytes in both the epidermal granular and cornified layers in psoriasis (Perera *et al.*, 2012).

Angiogenesis has a key role in the pathogenesis of psoriasis, but as yet research into antiangiogenic therapies for this chronic inflammatory condition has been limited (Schonthaler *et al.*, 2009). Vascular endothelial growth factor (VEGF), the most potent angiogenic factor, and its receptors, VEGFR-1 and VEGFR-2, are overexpressed by psoriatic papillary dermal microvascular endothelial cells (Detmar *et al.*, 1994). Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis (Xia *et al.*, 2003). We further define the overexpression of VEGFRs, including VEGFR-1, VEGFR-2, and VEGFR-3, in lesional psoriatic epidermal keratinocytes (Man *et al.*, 2008). The anti-VEGFR-2 antibody reduced the vessels in SCID-psoriasis xenograft and the PASI and thickness of epidermis in imiquimod-induced Balb/c psoriasiform skin (Figure 1). Both calcium and VEGF regulate VEGFR expression in psoriatic epidermis. More importantly, calcium is a potential regulator for VEGFR independent of VEGF (Man *et al.*, 2008). In addition, systemic anti-VEGF treatment strongly reduces skin inflammation in a mouse model of psoriasis (Schonthaler *et al.*, 2009). Valpha, a protein targeting VEGF-A and TNF-α showing double anti-angiogenic and anti-inflammatory effect, alleviates inflammation in a mouse model of psoriasis by normalizing the hyperplastic epidermis and vascular abnormalities (Jung *et al.*, 2011).

Pituitary tumor transforming gene 1 (*PTTG1*) could promote tumor angiogenesis. PTTG1 expression is enhanced in the psoriatic epidermis and induces TNF-α production from keratinocytes (Ishitsuka *et al.*, 2013). Our data have shown that PTTG1 in psoriatic epidermis is about 5-fold of normal ones. Different cell cycle of psoriatic keratinocytes expresses different amount of PTTG1 correlates with Cyclin B1 (Cai *et al.*, 2014). Further investigation should be done to clarify the role of PTTG1 in the pathogenesis of psoriasis.

Disrupted balance of angiogenic and antiangiogenic signals contributes to the proliferation of psoriatic keratinocytes. VEGF antagonist, PEDF (Pigment epithelium-derived factor), has an inhibitory role in proliferation and migration of keratinocytes. Topical application of anti-angiogenic peptides based on pigment epithelium-derived factor reduced epidermal thickness and angiogenesis (Abe *et al.*, 2010). Intradermal PEDF administration reduced the thickness and angiogenesis of grafted epidermis in xenotransplanted SCID mice (Abe *et al.*, 2010). We have found PEDF in psoriatic keratinocytes is elevated, and PEDF has an inhibitory role in proliferation and migration of HaCaT cells, a keratinocyte cell line (Li *et al.*, 2011). Therefore, the elevation of PEDF may be an anti-inflammatory system in patients with psoriasis (Nakajima *et al.*, 2012).

Inflammatory signal pathways, including MAPK pathway, Glucocorticoid and glucocorticoid receptor (GR), Sonic Hedgehog (Shh)/Gli pathway, are involved in the pathogenesis of psoriasis. VEGF induces proliferation of human epidermal keratinocytes and hair follicle dermal papilla cells through VEGFR-2-mediated activation of ERK (Man *et al.*, 2006; Li *et al.*, 2012). Topical glucocorticoids are the first-line drugs for inflammatory diseases of the skin. The efficacy of glucocorticoids results from the pleiotropic effects of the GR on multiple signaling pathways in many target tissues. Keratinocyte-targeted overexpression of GR delays cutaneous wound healing and reduces migration and increases differentiation of keratinocytes (Sanchis *et al.*, 2012). Epidermal inactivation of GR triggers skin barrier defects and cutaneous inflammation (Sevilla *et al.*, 2013). In normal skin and cultured human epidermal keratinocytes, intracellular GR is localized in the nuclei, while in psoriatic skin and cultured keratinocytes, GR is in the cytoplasm. VEGF

[1]*Department of Dermatology, Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang, China*

Correspondence: Min Zheng or Xiao-Yong Man, Department of Dermatology, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China. E-mail: minz@zju.edu.cn or manxy@zju.edu.cn

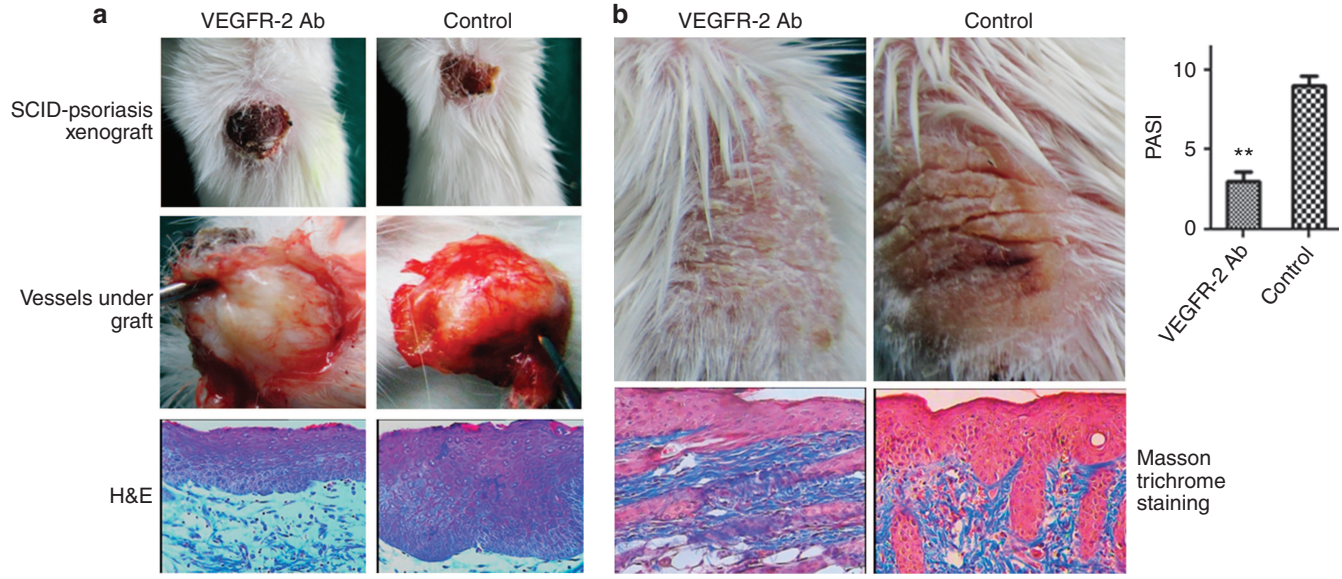

Figure 1. Effect of an anti-VEGFR-2 antibody (Ab) on psoriatic lesions. (**a**) The anti-VEGFR-2 antibody reduced the vessels and thickness of the epidermis in SCID-psoriasis xenograft. (**b**) The Anti-VEGFR-2 antibody reduced the PASI (**$P<0.01$) and thickness of epidermis in imiquimod-induced Balb/c psoriasiform skin.

and IFN-γ led to impaired nuclear translocation of GR through p53 and microtubule-inhibitor, vincristine, and inhibited nuclear uptake of GR in normal keratinocytes. In addition to dexamethasone, IL-13 was also able to transfer GR into nuclei of psoriatic keratinocytes. Furthermore, discontinuation of dexamethasone induced cytoplasmic retention of GR in normal keratinocytes (Man *et al.*, 2013). Impaired nuclear translocation of GR is associated with VEGF, IFN-γ, p53, and microtubule. Therapeutic strategies designed to accumulate GR in the nucleus, such as IL-13, may be beneficial for the therapy of psoriasis (Man *et al.*, 2013).

Inhibition of microtubule assembly also upregulates BMP-2 expression and enhances Gli2 protein concentrations in osteoblasts (Zhao *et al.*, 2009). Glis are the primary transcription factors that mediate Sonic hedgehog (Shh) signals in the mouse. Gli1 and Gli2 are mostly regarded as a transcriptional activator, while Gli3 mainly acts as a transcriptional repressor. Glucocorticoids can specifically modulate Smo ciliary accumulation, and there is a potential crosstalk of glucocorticoids and the Hedgehog pathway (Wang *et al.*, 2012). In psoriatic skin, Gli1 is overexpressed and may decrease neurofibromin expression (Endo *et al.*, 2006). However, a recent study showed that absence of elevated Hh target gene expression in lesional psoriatic skin, which indicates that the Hh pathway is not activated in this disease, raising questions regarding the proposed use of Hh antagonists as antipsoriatic agents (Gudjonsson *et al.*, 2009). To further define the role of Hh signals in psoriasis, real-time PCR was performed and showed increased expression of Shh, Kif7, and Gli1, and decreased SUFU and Gli3 ($P<0.001$) of RNA isolated from epidermis. However, from whole skin, no difference of Shh, Kif7, Gli1, and Gli3 was detected, only decreased SUFU was detected. So, it seems that further investigation of the role of Hh signals in psoriasis should be done.

VEGF-A promotes IL-17 A-producing γδ T-cell accumulation in mouse skin and serves as a chemotactic factor for plasmacytoid dendritic cells (Suzuki *et al.*, 2014). Corticosteroid suppresses VEGF-A in infantile hemangioma-derived stem cells (Greenberger *et al.*, 2010). In addition, overexpression of PTTG1 in keratinocytes induces the production of TNF-a, and TNF-α induces PTTG1 expression (Ishitsuka *et al.*, 2013). Therefore, there is a link of angiogenic and inflammatory signals.

In conclusion, the balance between angiogenic and angiostatic factors has important roles in psoriasis. Inflammatory signal pathways, glucocorticoids and their receptor, and MAPK and Hedgehog/Gli pathways are involved in the pathogenesis of psoriasis and therapeutic target for psoriasis. The angiogenesis and inflammatory pathways may form a complex net to control the onset and maintain psoriasis.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

This work was supported by the grants from the National Natural Science Foundation of China (NSFC) (81171496, 81171497, 81371740, and 81371741).

REFERENCES

Abe R, Yamagishi S, Fujita Y *et al.* (2010) Topical application of anti-angiogenic peptides based on pigment epithelium-derived factor can improve psoriasis. *J Dermatolol Sci* 57: 183–91

Cai SQ, Dou TT, Li W *et al.* (2014) Involvement of pituitary tumor transforming gene 1 in psoriasis, seborrheic keratosis, and skin tumors. *Discov Med* 18:289–99

Detmar M, Brown LF, Claffey KP *et al.* (1994) Overexpression of vascular permeability factor/vascular endothelial growth factor and its receptors in psoriasis. *J Exp Med* 180:1141–6

Endo H, Momota Y, Oikawa A *et al.* (2006) Psoriatic skin expresses the transcription factor Gli1: possible contribution of decreased neurofibromin expression. *Br J Dermatol* 154:619–23

Greenberger S, Boscolo E, Adini I *et al.* (2010) Corticosteroid suppression of VEGF-A in infantile hemangioma-derived stem cells. *N Engl J Med* 362:1005–13

Gudjonsson JE, Aphale A, Grachtchouk M *et al.* (2009) Lack of evidence for activation of the hedgehog pathway in psoriasis. *J Invest Dermatol* 129:635–40

Ishitsuka Y, Kawachi Y, Maruyama H *et al.* (2013) Pituitary tumor transforming gene 1 induces tumor necrosis factor-alpha production from keratinocytes: implication for involvement in the pathophysiology of psoriasis. *J Invest Dermatol* 133:2566–75

Jung K, Lee D, Lim HS *et al.* (2011) Double anti-angiogenic and anti-inflammatory protein Valpha targeting VEGF-A and TNF-alpha in retinopathy and psoriasis. *J Biol Chem* 286:14410–8

Li CM, Li W, Man XY *et al.* (2011) Pigment epithelium-derived factor plays an inhibitory role in proliferation and migration of HaCaT cells. *Mol Biol Rep* 38:2099–105

Li W, Man XY, Li CM *et al.* (2012) VEGF induces proliferation of human hair follicle dermal papilla cells through VEGFR-2-mediated activation of ERK. *Exp Cell Res* 318:1633–40

Man XY, Li W, Chen JQ *et al.* (2013) Impaired nuclear translocation of glucocorticoid receptors: novel findings from psoriatic epidermal keratinocytes. *Cell Mol Life Sci* 70:2205–20

Man XY, Yang XH, Cai SQ *et al.* (2008) Overexpression of vascular endothelial growth factor (VEGF) receptors on keratinocytes in psoriasis: regulated by calcium independent of VEGF. *J Cell Mol Med* 12: 649–60

Man XY, Yang XH, Cai SQ *et al.* (2006) Immunolocalization and expression of vascular endothelial growth factor receptors (VEGFRs) and neuropilins (NRPs) on Keratinocytes in human epidermis. *Mol Med* 12:127–36

Nakajima H, Nakajima K, Tarutani M *et al.* (2012) The role of pigment epithelium-derived factor as an adipokine in psoriasis. *Arch Dermatol Res* 304:81–4

Nestle FO, Kaplan DH, Barker J (2009) Psoriasis. *N Engl J Med* 361:496–509

Perera GK, Di Meglio P, Nestle FO (2012) Psoriasis. *Ann Rev Pathol* 7:385–422

Sanchis A, Alba L, Latorre V *et al.* (2012) Keratinocyte-targeted overexpression of the glucocorticoid receptor delays cutaneous wound healing. *PLoS One* 7:e29701

Schonthaler HB, Huggenberger R, Wculek SK *et al.* (2009) Systemic anti-VEGF treatment strongly reduces skin inflammation in a mouse model of psoriasis. *Proc Natl Acad Sci USA* 106:21264–9

Sevilla LM, Latorre V, Sanchis A *et al.* (2013) Epidermal inactivation of the glucocorticoid receptor triggers skin barrier defects and cutaneous inflammation. *J Invest Dermatol* 133:361–70

Suzuki T, Hirakawa S, Shimauchi T *et al.* (2014) VEGF-A promotes IL-17 A-producing gamma delta T cell accumulation in mouse skin and serves as a chemotactic factor for plasmacytoid dendritic cells. *J Dermatol Sci* 74:116–24

Wang Y, Davidow L, Arvanites AC *et al.* (2012) Glucocorticoid compounds modify smoothened localization and hedgehog pathway activity. *Chem Biol* 19:972–82

Xia YP, Li B, Hylton D *et al.* (2003) Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis. *Blood* 102:161–8

Zhao M, Ko SY, Liu JH *et al.* (2009) Inhibition of microtubule assembly in osteoblasts stimulates bone morphogenetic protein 2 expression and bone formation through transcription factor Gli2. *Mol Cell Biol* 29: 1291–305